

Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claim 1 has been amended, claims 3 and 6 have been cancelled without prejudice, and new claims 14-21 have been added. Descriptive support for new claim 14 appears in the first full paragraph on page 30 and the third full paragraph on page 35; descriptive support for new claim 15 appears in the first full paragraph on page 34; and descriptive support for new claim 16 appears in the first full paragraph on page 30. New claim 17 finds descriptive support in original claim 3 (i.e., claim written in independent form), and new claims 18-21 find descriptive support in original claims 3 and 8-13. Claims 1, 2, 4, 5, and 7-21 are pending, with claims 4 and 5 being withdrawn.

The amendments to the specification are made to correct typographical errors. In particular, the paragraph on page 103 is corrected to render the specification internally consistent. The specification at page 58, lines 17-18, clearly recites that *holB* was not identified by Deckert et al., 1998. Therefore, correction of the paragraph on page 103 does not constitute new matter.

Applicants respectfully request reconsideration of the restriction requirement imposed in the present application. Because of the relatedness of the subunits and their use together in a clamp loader complex (see, e.g., claims 9 and 19), applicants submit that the search of the related subcombinations would not be burdensome.

The objection to the specification is overcome by the above amendments. Although applicants disagree with the assertion made by the U.S. Patent and Trademark Office (“PTO”), the present claim language is clearly supported by the first full paragraph on page 30, along with the disclosure of the nucleic acid sequence of SEQ ID NO: 177 (and SEQ ID NOS: 179 and 181) and the corresponding amino acid sequence of SEQ ID NO: 178 (and SEQ ID NOS: 180 and 182).

The objections to claims 1, 3, and 6 are overcome by the above amendments and should be withdrawn. The objection to claims 1-13 as encompassing non-elected subject matter is noted, but no amendments have been made in this regard given applicants’ request for reconsideration (above).

The rejection of claim 7 under 35 U.S.C. §112 (second paragraph) for indefiniteness is respectfully traversed. The PTO has taken the position that the term “purified” is unclear in view of the language “isolated” as used in claim 1. Applicants respectfully disagree.

The term “isolated” connotes that the claimed subunit is in an environment that is distinct from that of the native subunit, i.e., the subunit no longer exists in a cellular environment. In contrast to a subunit that can exist, for example, in a protein extract obtained from a cell, a purified subunit is one that is substantially separated from other proteins. Both isolated delta subunit and purified delta subunit are described in the procedure recited in Example 19 for the recombinant expression of *A. aeolicus* delta subunit. In particular, Example 19 describes cell lysate containing the recombinant delta subunit (i.e., isolated but not yet purified protein), as well as the purification of delta subunit from the cell lysate (first via Heparin Agarose column and then via FFQ Sepharose column). Thus, “purified” and “isolated” are distinct terms, and persons of skill in the art would understand the distinction between these two terms.

For these reasons, the rejection of claim 7 is improper and should be withdrawn.

The rejection of claims 1, 2, and 4-13 under 35 U.S.C. §112 (first paragraph) as lacking written descriptive support is respectfully traversed.

The burden of establishing that an application lacks adequate written descriptive support falls on the PTO. *See In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.”). Hence, the PTO must demonstrate *why* the disclosure is insufficient.

The Federal Circuit has clearly espoused that *per se* conclusions of written description violations cannot be founded upon the basis of genus size alone. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1326-27, 63 USPQ2d 1609, 1614-15 (Fed. Cir. 2002) (refusing to adopt position that three species as a matter of law cannot satisfy written description requirement for significantly larger genus). Thus, the PTO’s conclusion cannot be based on genus size alone. But that is precisely what the PTO has done at page 5 of the outstanding office action. Because the PTO’s position is unsupported by law and

unsupported by any facts other than genus size, applicants submit that the PTO's position cannot be sustained.

In contrast, applicants present Exhibits 1-3 (attached hereto) as evidence that the nucleic acid sequence of SEQ ID NO: 177 and the corresponding amino acid sequence of SEQ ID NO: 178 represent the claimed genus. Exhibit 1 is a presentation of a Genbank accession for a thermophilic *Bacillus*, or *Geobacillus*, *hola* nucleic acid that is homologous to the nucleotide sequence of SEQ ID NO: 177. This *hola* nucleic acid was identified by a protein-protein BLAST search of the Genbank database performed using the amino acid sequence of SEQ ID NO: 178 and the BLAST default settings. Based upon alignments performed using Align[®] for nucleic acids and ClustalW for amino acids (using the European Molecular Biology Laboratory server and its default settings), this homolog shares about 98 percent identity at the nucleic acid level (Exhibit 2) and about 99 percent identity at the amino acid level (Exhibit 3). Thus, species of delta subunits from thermophilic organisms that belong to the biological classification *Bacillus* or *Geobacillus* clearly share similar structure and, therefore, function.

Applicants submit that the language recited in claim 1 is precisely the type of claim language that was acknowledged in *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) as being acceptable under the written description requirement. In *Eli Lilly*, the Federal Circuit addressed the validity of several claims of U.S. Patent No. 4,652,525 to Rutter et al. ("Rutter"), specifically those claims that recited the limitations 'vertebrate,' 'mammalian,' or 'human' cDNA for insulin. Rutter disclosed the nucleotide and amino acid sequences of a rat cDNA encoding insulin, and described a general procedure for obtaining the human cDNA encoding insulin. *Id.* at 1567, 43 USPQ2d at 1405. The Federal Circuit found that the description of the rat cDNA did not provide adequate descriptive support for the narrow subgenus of 'human' cDNA (no species disclosed), the larger subgenus of 'mammalian' cDNA (only the one rat species disclosed), and the larger genus of 'vertebrate' cDNA (only the one rat species disclosed). *Id.* at 1567-68, 43 USPQ2d at 1405. The Federal Circuit did acknowledge, however, the district court's statement that the specification provided adequate written descriptive support for the subgenus of 'rat' cDNA encoding insulin. *Id.* at 1566.

Thus, functional language should be acceptable when the genus as claimed is sufficiently limited in scope (i.e., from *Bacillus* or *Bacillus stearothermophilus*) and the specification describes one or more species within that genus. Claim 1 recites the same type of functional claim language that was identified as acceptable in *Eli Lilly* given the

description of a single species by its nucleotide sequence. Thus, it should be evident that claim 1 (and claims dependent thereon) finds written descriptive support in the present application.

As demonstrated by Exhibits 1-3, one of ordinary skill in the art would have understood that applicants were in possession of the presently claimed invention at the time the present application was filed. This is so, because persons of skill in the art would have expected sufficiently related organisms from the genus *Bacillus* (and now *Geobacillus*) to possess homologous *holA* nucleotide sequences or delta subunit proteins. Exhibits 1-3 confirm this expectation to have been reasonable.

In view of all of the foregoing, applicants submit that the rejection of claims 1, 2, and 4-13 is improper and should be withdrawn.

The rejection of claims 1, 2, and 4-13 under 35 U.S.C. §112 (first paragraph) for lack of enablement is respectfully traversed.

It is the position of the PTO that the specification does not provide sufficient guidance for making and using other delta subunits within the scope of the claims. Applicants respectfully disagree.

The PTO is respectfully reminded that all that is needed is objective enablement of what is claimed. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The present application provides the nucleotide sequence of *Bacillus* (now *Geobacillus*) *stearothermophilus holA* (e.g., SEQ ID NO: 177) and describes how one of ordinary skill can isolate homologs of the disclosed sequence (*see* page 41, line 9 to page 42, line 29), express the delta subunit encoded by such homologous *holA* sequences (*see* Example 19, expressing *A. aeolicus* delta subunit), and test the encoded delta subunit for clamp loader assembly competence (*see* Examples 24 and 25, testing *A. aeolicus* clamp loader assembly) and for clamp loader activity (*see* Examples 26 and 30, testing *A. aeolicus* clamp loader activity). Thus, one of ordinary skill in the art would have been fully able to make and use DNA molecules and their encoded proteins within the scope of the presently claimed invention.

Moreover, with regard to method 3 for homolog identification, described at page 42, that is precisely the approach used to identify the *holA* homolog shown in Exhibit 1 (i.e., from other *Bacillus* or *Geobacillus* organisms). For this reason, it should be apparent that the present application fully enables the production and use of other species of *Bacillus* or *Bacillus* (now *Geobacillus*) *stearothermophilus holA* homologs.

In view of all of the foregoing, applicants submit that the rejection of claims 1, 2, and 4-13 for lack of enablement is improper and should be withdrawn.

Because 1 is allowable for the reasons noted above, applicants further submit that new claims 14-16 also are allowable. Because previous claim 3 was not rejected, applicants submit that new claims 17-21 are allowable.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 1, 2006

/Edwin V. Merkel/

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Exhibit 1

NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Books

My NCBI [Sign In] [Registered]

Search Nucleotide

for

Go

Clear

Limits

Preview/Index

History

Clipboard

Details

Display GenBank(Full) Show 5 Send to

Range: from 2532557 to 2533603

Show whole sequence

☐ Reverse complemented strand Fer☐ 1: BA000043. Reports *Geobacillus kaustophilus* [gi:56378377]

Links

Features Sequence

LOCUS BA000043 1047 bp DNA linear BCT 04-DEC-2004

DEFINITION *Geobacillus kaustophilus* HTA426 DNA, complete genome.

ACCESSION BA000043 REGION: 2532557..2533603

VERSION BA000043.1 GI:56378377

KEYWORDS

SOURCE *Geobacillus kaustophilus* HTA426

ORGANISM *Geobacillus kaustophilus* HTA426

Bacteria; Firmicutes; Bacillales; Bacillaceae; *Geobacillus*.

REFERENCE 1

AUTHORS Takami,H., Takaki,Y., Chee,G.J., Nishi,S., Shimamura,S., Suzuki,H., Matsui,S. and Uchiyama,I.

TITLE Thermoadaptation trait revealed by the genome sequence of thermophilic *Geobacillus kaustophilus*

JOURNAL (er) Nucleic Acids Res. 32 (21), 6292-6303 (2004)

PUBMED 15576355

REFERENCE 2 (bases 1 to 1047)

AUTHORS Takami,H., Takaki,Y. and Chee,G.

TITLE Direct Submission

JOURNAL Submitted (25-JUN-2003) Hideto Takami, Japan Marine Science and Technology Center, Microbial Genome Analysis Research Group; 2-15 Natsushima-cho, Yokosuka, Kanagawa 237-0061, Japan (E-mail:takamih@jamstec.go.jp, URL:http://www.jamstec.go.jp/jamstec-e/bic/exbase.html, Tel:81-46-867-9643, Fax:81-46-867-9645)

FEATURES

source Location/Qualifiers

1..1047

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/strain="HTA426"

/isolation_source="isolated from the deepest Ocean"

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/note="thermophile"

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/locus_tag="GK2513"

CDS complement(1..1047)

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/transl_table=11

/product="hypothetical conserved protein"

/protein_id="BAD76798.1"

/db_xref="GI:56380890"

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REWNLAVIDCEETPVEAALEEAETVPPFGERRVILIKHPYFFTSEKEKEIEHDLAKLE
AYLKAPSPFSIVVFFAPYEKLDERRKKITKLAKESQEVVIAAPLAEAEALRAWVRRRIES
QGAQASDEAIDVLLRRAGTQLSALANEIDKLALFAGSGGTIEAAVERLVARTPEENV
FVLVEQVAKRDI PAALQTFYDLENNEEPIKILALLAAHFRLLSQVKWLASLGYGQAQ
IAAALKVHPFRVKLALAAQARFADGELAEAINELADADYEKSGAVDRRLAVELLIMR

WGTRFAQAGRHGRR"

ORIGIN

```
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121 ctcgtagatc gcttcagcaa gctctccgtc agcgaagcgg gccgcttgag caagagcgag
181 cttgacgcgg aacgggtgca ccttgagcgc cgcagcaatt tgcgcctgcc cgtagcctaa
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301 tttgatcggc tcttcattgt ttcaagcag atcataaaac gtctgcaacg ccgctggaat
361 gtcgcgcttc gccactigct cgacaagcac aaatacgttt tcttcggggc tgggggcgac
421 aagcggttca accgcggcgg cctcgatggt tccggccgat ccggcaaaaca gggocaaattt
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1021 aatgtttccc catacgcggt ccagcat
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Aug 15 2006 13:27:38

Exhibit 2

Program: needle
Rndate: Wed Aug 23 05:38:23 2006
Align format: srspair
Report_file: /ebi/externserv/old-work/needle-20060823-05382266461273.output
#####

Aligned_sequences: 2
1: SEQ_177
2: G_kaustophilus
Matrix: EBIOSUM62
Gap_penalty: 10.0
Extend_penalty: 0.5

Length: 1047
Identity: 1030/1047 (98.4%)
Similarity: 1030/1047 (98.4%)
Gaps: 3/1047 (0.3%)
Score: 6325.0

#####

SEQ_177	1	ATGCTGGAACGCGTATGGGGAACATTGAAAAACGGCGTTTTCCTCCCT	50
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SEQ_177	51	TTATTTATTATACGGCAATGAGCCGTTTTTATTAACGGAAACGTATGAGC	100
G_kaustophilus	51	ttatattatatacggcaatgagccgtttttattaacggaaacgtatgagc	100
SEQ_177	101	GATTGGTGAACGCAGCGCTTGGCCCCGAGGAGCGGGAGTGAACCTGGCT	150
G_kaustophilus	101	gattggtgaacgcagcgcttggccccgaggagcgaggagtgaacttggct	150
SEQ_177	151	GTGTACGACTGCGAGGAAACGCCGATCGAGGCGGCGCTTGAGGAGGCCGA	200
G_kaustophilus	151	gtgtacgactgcgaggaaacgccggtcgaggcgcgcttgaggaggccga	200
SEQ_177	201	GACGGTGCCGTTTTTCGGCGAGCGGCGTGTCATTCTCATCAAGCATCCAT	250
G_kaustophilus	201	gacggtgcccgtttttcggcgagcgcggtgtcatccatcaagcatccat	250
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G_kaustophilus	351	cgcgcgtacgagaagcttgatgagcgaaaaaaattacgaagctcgcca	400
SEQ_177	401	AAGAGCAAAGCGAAGTCGTATCGCCGCCCGCTCGCCGAAGCGGAGCTG	450
G_kaustophilus	401	aagagcaaagcgaagtcgtatcgccgcccgctcgccgaagcggagctg	450
SEQ_177	451	CGTGCCCTGGGTGCGGCGCCCGCATCGAGAGCCCAAGGGGCGCAAGCAAGCGA	500
G_kaustophilus	451	cgcgctgggtgcgcgcccgcatcgagagccaagggcgcaagcaagcga	500

SEQ_177	501	CGAGGCGATTGATGTCCTGTTGCGGCGGGCGGGGACGCAGCTTTCCGCCT	550
G_kaustophilu	501	cgaggcgattgatgtcctgttgcgcgggcggggacgcagctttccgcct	550
SEQ_177	551	TGGCGAATGAAATCGATAAATTGGCCCTGTTTGCCCGATCGGGCGGAACC	600
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SEQ_177	751	TTGGCGTTGCTCGCCGCCCATTTCCGCTTGTCTTCGCAAGTGAAATGGCT	800
G_kaustophilu	751	ttggcgctgctcgccgcccatttccgcttgtcttcgcaagtgaatggct	800
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SEQ_177	951	GAAAAGCGGGCGGTCGATCGCCGGTTGGCCGTTGAGCTGCTTCTGATGC	1000
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SEQ_177	1001	GCTGGGGCGCCCGCCCGCGCAAGCGGGCGCCACGCGCCGCGG	1044
G_kaustophilu	1001	ggtggggcaccgcgcccggcgcaagcggggcgctcacggccggcggtga	1047

Exhibit 3

CLUSTAL W (1.83) Multiple Sequence Alignments

Sequence format is Pearson

Sequence 1: SEQ_178 348 aa

Sequence 2: G_kaustophilus 348 aa

Start of Pairwise alignments

Aligning...

Sequences (1:2) Aligned. Score: 99

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Start of Multiple Alignment

There are 1 groups

Aligning...

Group 1: Sequences: 2 Score:7434

Alignment Score 2093

CLUSTAL-Alignment file created [/ebi/externserv/clustalw-work/interactive/clustalw-20060823-05445443.aln]

```

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SEQ_178          GELAEAINELADADYEVKSGAVDRRLAVELLMRWGARPAQAGRHR 348
G_kaustophilus  GELAEAINELADADYEVKSGAVDRRLAVELLMRWGTRPAQAGRHR 348
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